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CAUSES OF INFECTED PANCREATIC NECROSIS AFTER SEVERE ACUTE PANCREATITIS

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Abstract:

Necrotizing pancreatitis is an inflammatory disease clinically changes from mild interstitial edema of the pancreas to extreme type of pancreatic necrosis and hemorrhage.

Study design and setting: *Descriptive case study; Surgical floor of Mayo Hospital, Lahore.*

Duration: *It was a six months study*

Method: *A total of 105 patients with age range 40-75 year were included using random sampling technique. Demographic history was obtained from the patients included in this study and patients were followed for 2-6 weeks with an abdominal CT scan to check for pancreatic necrosis and CT-guided fine-needle aspiration cytology [FNAC] to verify infection. The contributing factors such as gallstone, alcoholism, trauma, and malignancy were evaluated in every patient [both with and without infected pancreatic necrosis] as per surgical definition. The CT severity index was used to predict adverse outcome, such as mortality with pancreatic necrosis. Ranson scoring system was used to determine prognostic signs for clinical severity and rating of acute pancreatitis.*

Results: *The bacterial culture was found positive in 37[35.2%] patients, gall stone was present in 41[39.0%] cases and choledocholithiasis was present in 30.5% patients. According to this study, the idiopathy was present in 36 [34.3%] cases and the infection was noted in 32[30.5%] cases. In conclusion, the prevalence of the infected acute pancreatitis was 30.5%.*

Keywords: *Infection, severe acute pancreatitis, CT, Ranson, gall-stone, idiopathic.*

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INTRODUCTION:

Acute pancreatitis is an inflammatory disease that causes mild interstitial edema of the pancreas and can lead to severe pancreatic hemorrhage and necrosis. [1] In acute pancreatitis, within 14 days, inflammatory mediators are released which lead to systemic inflammatory response syndrome [SIRS].

In the absence of infection, organ dysfunction as well as other disorders, such as increased permeability of capillary, hypovolemia, fluid loss from the intravascular space and hyperdynamic circulatory regulation, occurs. In the second phase, after two weeks of beginning of the disease, infection of pancreatic necrosis leads to sepsis-related complications. [2] It is related to multiple systemic complications, such as cardiovascular, renal and pulmonary failure.

By Atlanta classification, severe acute pancreatitis [SAP] is characterized as an AP connected with systemic complications. This classification is a clinically based group characterizing AP complications and severity. Failure in organ functioning within 72 h of the side effects onset is characterized as an early severe acute pancreatitis [ESAP]. ESAP is characterized is by an increasing MODS, short course, early hypoxemia, expanded rate of malfunction of abdominal compartment disorder [ACS]. Pancreatic necrosis, multiorgan dysfunction syndrome, sepsis and infection, cause the mortality in acute pancreatitis. Necrosis in the pancreas causes infection which becomes the main reason of late mortality. Renal failure [RF], cardiovascular [CVF] and acute respiratory failure [ARF], can forecast the deadly result in severe acute pancreatitis. [3] Most of the mortalities [20-40%] have been reported due to severe acute pancreatitis. In acute pancreatitis, premature activation of pancreatic enzymes inside the pancreas leads to autodigestion of the gland and inflammation. The pancreatic enzymes enter the bloodstream and stimulate the production of inflammatory tumor necrosis factor-α [TNF- α] and inflammatory cytokines. Due to the release of the pancreatic enzymes, it triggers an inflammatory flow leading to systemic inflammatory response syndrome. Correct diagnosis of severe acute pancreatitis at the time of hospital admission, quick SAP characterization is of great importance.

In the USA, nearly 185,000 cases of pancreatitis are reported every year. Necrotizing pancreatitis leads to high mortality rate causing 40-70% deaths. [4] Due to complications caused by this debilitating disease nearly one half of the patient dies due to necrotizing pancreatitis & approximately 30% patient die with infection. While acute necrotizing pancreatitis causes deaths only in 10-15% patients. [5]

In the 1980s three patterns evolved for the surgical treatment of necrotic acute and infective pancreatitis. These involved necrosectomy, lavage, and laparostomy [open abdominal management]. [6]

There are many causes of acute pancreatitis but most common are excessive the use of excessive alcohol consumption or the presence of gallstone. Frequency of acute pancreatitis varies geographically. Common causes in the United Kingdom and Asia are due to gallstones, while in the USA and Finland most causative agent is alcohol consumption. The idiopathic group still consists of 10-30% cases. Interest is focused on biliary sludge, as reporte, it is present in 70% patients suffering from acute pancreatitis with idiopathic acute pancreatitis. While rest of the 10% cases are of miscellaneous etiologies and there are many different kinds of inducing agents. [7]

Most of the deaths occur due to complications like infection of pancreatic necrosis and bacteria. Previous studies have found an important link between acute pancreatitis and genetic factors, but studies involved comparatively small cohorts. All these data showed a positive link between recurrent and acute pancreatitis. Malfunction gastrointestinal mucosal barrier is present because it allows translocation of bacteria that leads to severe inflammation, infection and many other complications. Few reports are available about the reason and physiology of failure in mucosal barrier in the case of acute pancreatitis that may lead to the initiation of this disease. Failure in tight junction within the pancreas may be an important reason for the early development of acute pancreatitis. [8]

Gallstones and alcohol misuse are the main and important reasons for acute pancreatitis. During the past 20-30 years, however, the risk of biliary pancreatitis is unlikely to be more than 2% in patients with asymptomatic gallstones and that of alcoholic pancreatitis is unlikely to exceed 2–3% in heavy drinkers. Other factors are genetic and therefore probably play their part. Indiscriminate use of drugs is also one of the important reason for acute pancreatitis.

Other etiologic factors include infectious diseases, traumatic acute pancreatitis, and hyperparathyroidism. The rationale for this study was

the absence of any report about the frequency of infected pancreatic necrosis after severe acute pancreatitis, and about the contributing factors for severe necrotizing pancreatitis.

MATERIALS AND METHODS:

This Descriptive case studies study was conducted in the North Surgical Ward of Mayo Hospital, Lahore, Pakistan. Duration of study was one month after the IRB approval for the study.

Sampling Technique was non-probability consecutive sampling. Sample size [n] was calculated using confidence level 95%, **P** = proportion of patients with infected pancreatic necrosis among patients presented with acute pancreatitis = 40% [9], **Q** = 100-P, d= 9.5 [permissible error for sampling variation] Sample size of 105 patients is estimated by using 5% level of significance. Inclusion criteria was: 'All patients with severe acute pancreatitis established with Revised Atlanta classification, of both genders, aged 21-80 years, were included. Ranson score was > 3.

Exclusion criteria was: Patients with recurrent or chronic pancreatitis [history of pain and positive CT scan findings], malignancy [on CT scan abdomen and biopsy], diabetes mellitus [Two Fasting BSL readings>125mg/dl or one random BSL>200mg/dl], and primarily treated at another hospital was excluded.

Non-gallstone pancreatitis

At admission: During initial 48hr

1. Age >55 yr
2. Absolute decrease in hematocrit value >10%
3. white-cell count >16,000/mm^3
4. Increase in BUN >5mg/dl[1.8mmol/L]
5. blood glucose >200 mg/dl [11.1 mmol/liter]
6. Serum calcium<8mg/dl[2mmol/L]
7. Serum LDH>350 IU/liter Arterial PaO_2<60mmHg
8. serum AST >250 IU/liter Base deficit >4mmol/L
9. Fluid sequestration >6L

For **gallstone pancreatitis**, the parameters are:

At admission:

Within 48 hours :

1. Age in years > 70 years
2. 1.Haematocrit fall value > 10%
3. White blood cell count > 18000 cells/mm32; Serum calcium <8mg/dL
4. Blood glucose > 12.2 mmol/L [> 220 mg/dL] 3PaO_2 < 60 mmHg
5. Serum AST > 250 IU/L4BUNinc. by >2mg/dl or >7mmol/L
6. Serum LDH > 400 IU/L
7. Scoring: One point for each criterion was met.

The CT severity index was used to predict adverse outcome, such as mortality with pancreatic necrosis. Ranson score system was used to determine prognostic signs for clinical severity for acute pancreatitis. Data were entered and analyzed using IBM SPSS Statistics version 21 software. Continuous variables, such as age and Ranson score were described by mean [±SD] or median and categorical data like gender, infected pancreatic necrosis and contributing factors like gallstones, chronic alcohol consumption, choledocholithiasis, hypercalcemia, hypothermia, idiopathic, tumors and trauma were presented in frequency and percentages.

Table 1.1: Computed Tomography Severity Index

Fluid Collections	**Points**
Normal pancreas	0
Gland enlargement	1
Peripancreatic inflammation	2
One fluid collection	3
Multiple fluid collections	4
Necrosis	
<30%	2
30–50%	4
50%	6
Total	10

Score of <3 = 3% mortality rate. Score of >7= 17% mortality rate. Atleast 30% necrosis on CT scan abdomen signals severe acute pancreatitis.

RESULTS:

In the present study, a total of 105 cases were enrolled. The mean age of the patients was 49.67±16.99 years with minimum and age ranged 21-80 years as shown in Table 2.1.

Table 2.1: Descriptive statistics of age [years]

Age [years]	**N**	105
	Mean	49.67
	±SD	16.99
	Minimum	21
	Maximum	80

71 [67.62%] patients were males and 34 [32.38%] were females. The male to female ratio was 2.1:1 as shown in Figure 2.1**.**

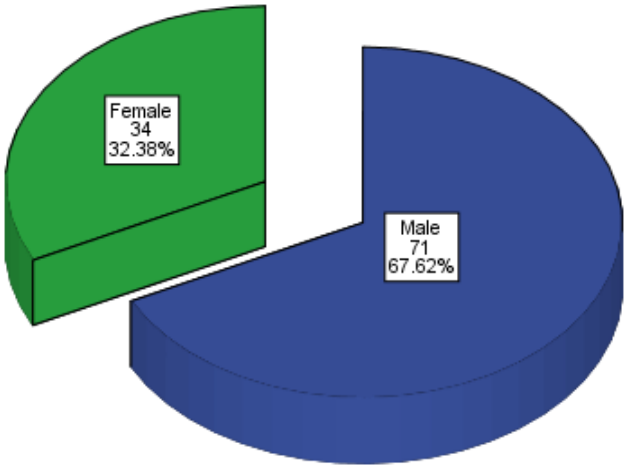

Figure 2.1: Frequency distribution by gender

The CT necrosis was absent in 34 [32.4%] patients and < 30% necrosis was detected in 28[26.7%] cases, while 30-50% necrosis was recorded in 18 [17.1%] cases and > 50% necrosis was found in 25 [23.8%] cases using the CT scan for necrosis as shown in Table 2.2.

Table 2.2: Frequency of necrosis detected by CT scan

		# Patients	%age
Necrosis detection by CT scan	**Absent**	34	32.4
	< 30%	28	26.7
	30 - 50%	18	17.1
	50%	25	23.8
	Total	**105**	**100.0**

Fever was observed only in 78 [74.3%] cases and it was not observed in 27 [25.7%] cases as shown in Table 2.3**.**

Table 2.3: Frequency of fever distribution

		# Patients	%age
Fever	**P**	78	74.3
	A	27	25.7
	Total	**105**	**100.0**

P = Present; A = Absent

The results also revealed the incidence of leukocytosis in 79 [75.2 %] cases and it was not noted in 26[24.8%] cases as shown in Table 2.4.

Table 2.4: Frequency of Leukocytosis

		# Patients	%age
Leukocytosis	**P**	79	75.2
	A	26	24.8
	Total	**105**	**100.0**

P = Present; A = Absent

Abdominal pain was reported by 72.38% patients and it was not found in 27.63% patients as shown in Figure 2.2.

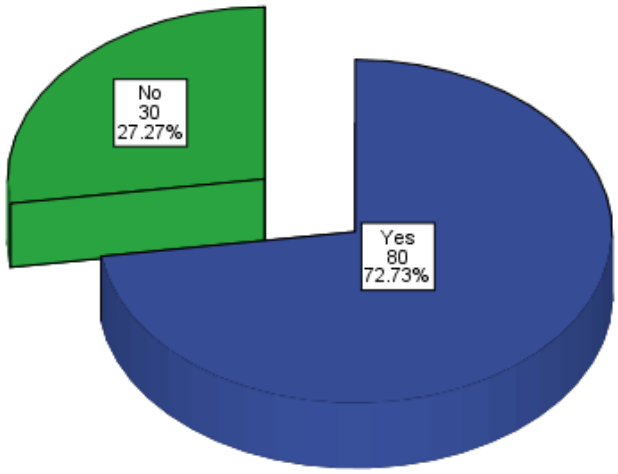

Figure 2.2: Frequency distribution of abdominal pain

Bacterial culture was found to be positive in 37 [35.2%] patients, while it was negative in 68 [64.8%] patients as shown in Table 2.5.

Table 2.5: Frequency of bacterial culture

		# Patients	%age
Bacterial Culture	**+ve**	37	35.2
	-ve	68	64.8
	Total	**105**	**100.0**

The fungal culture was noted positive in 34 [35.2%] patients only and it was noted negative in 71 [67.6%] patients as shown in Table 2.6.

Table 2.6: Frequency of fungal culture

		# Patient	%age
Fungal culture	**+ve**	34	32.4
	-ve	71	67.6
	Total	**105**	**100.0**

The gall stone was present in 41 [39.0%] cases and was absent in 64 [61.0%] cases as shown in Table 2.7.

Table 2.7: Frequency of gall stone

		# Patient	%age
Gall stone	**P**	41	39.0
	A	64	61.0
	Total	**105**	**100.0**

P = Present; A = Absent

Chronic alcohol consumption was recorded in 25 [23.8%] patients only and it was absent in 80 [76.2%] patients as shown in Table 2.8.

Table 2.8: Frequency of chronic alcohol consumption

		# Patients	%age
Chronic alcohol Consumption	**P**	25	23.8
	A	80	76.2
	Total	**105**	**100.0**

P = Present; A= Absent

Using CT scan, choledocholithiasis was found to be present in 30.5% of the total patients and it was absent in 69.5% patients as shown by CT scan as shown in Figure 2.3.

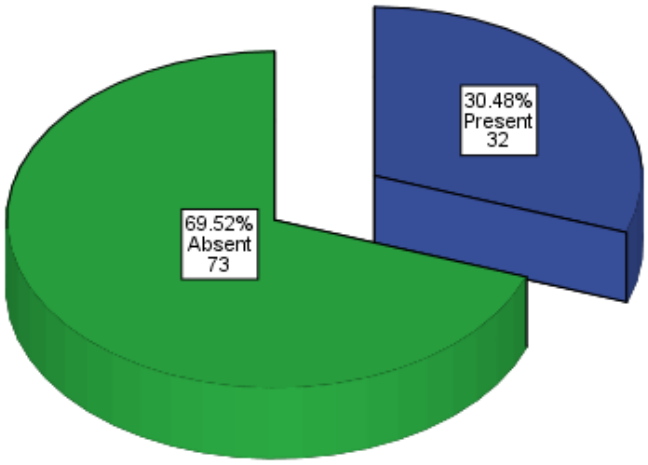

Figure 2.3: Frequency of choledocholithiasis

Hypercalcemia was present in 36 [34.3%] cases and it was absent in 69 [65.7%] cases as shown by CT scan as shown in Table 2.9.

Table 2.9: Frequency of hypercalcemia or hyperparathyroidism

		# Patients	%age
Hypercalcemia, Hyperparathyroidism	**P**	36	34.3
	A	69	65.7
	Total	**105**	**100.0**

P = Present; A = Absent

Hypothermia was present in 31 [29.5%] cases while 74 [70.5%] had normal body temperature as shown in Table 2.10.

Table 2.10: Frequency of hypothermia

		# Patients	%age
Hypothermia	**P**	31	29.5
	A	74	70.5
	Total	**105**	**100.0**

P = Present; A = Absent

Idiopathy was present in 36 [34.3%] cases and it was absent in 69 [65.7%] cases as shown in Table 2.11.

Table 2.11: Frequency of idiopathy

		# Patients [no.]	%age
Idiopathy	**P**	36	34.3
	A	69	65.7
	Total	**105**	**100.0**

P = Present; A = Absent

The study results showed that viral, bacterial, parasitic and fungal infection was present in 32 [30.5%] cases and it was not found in 73 [69.5%] cases as shown in Table 2.12.

Table 2.12: Frequency of infections

		# Patients	%age
Infections [i.e viral, bacterial, parasitic, fungal]	**P**	32	30.5
	A	73	69.5
	Total	**105**	**100.0**

P = Present; A = Absent

Pancreatic or ampullary tumor was present in 45 [42.9%] patients and it was absent in 60 [57.1%] patients as shown in Table 2.13.

Table 2.13: Frequency of pancreatic or ampullary tumors

		# Patients	%age
Pancreatic or ampullary tumors	**P**	45	42.9
	A	60	57.1
	Total	**105**	**100.0**

P = Present; A = Absent

In this study, traumatic conditions were found in 32.38% of patients and it was not found in 67.62% patients as shown in Figure 2.4.

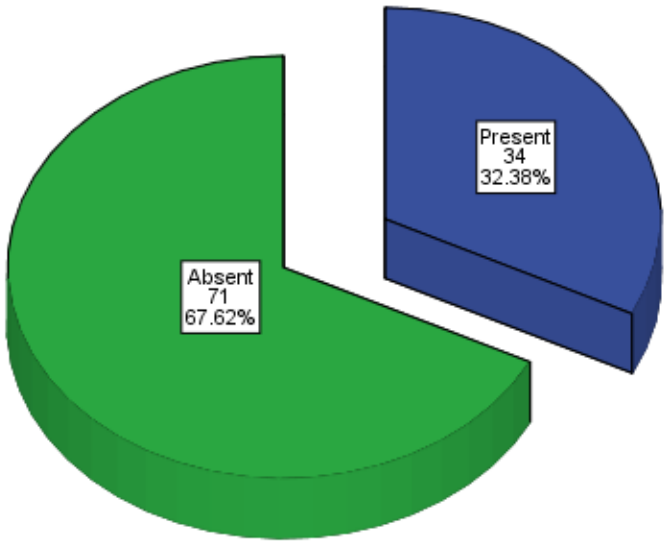

Figure 2.4: Frequency of trauma

In this study, pancreatic necrosis was absent in 34 cases; and in these patients, 2 cases showed infection and 28 cases showed <30% necrosis. While 9/28 cases had infection. Out of 18 cases with 30-50% necrosis, 11/18 had infection and out of 25 cases with >50% necrosis, infection was present in 10/25 cases. The difference was highly significant and cases with >30% necrosis showed significantly high infection rate i.e. p=0.000 as shown in Table 2.14.

Table 2.14: Comparison of infection in cases with different levels of pancreatic necrosis

		Infections		Total
		Present	Absent	
Pancreatic necrosis	Absent	2	32	34
	<30% necrosis	9	19	28
	30-50% necrosis	11	7	18
	>50% necrosis	10	15	25
Total		32	73	105

Chi-square test = 18.786
P-value = 0.000 [Highly significant]

In patients presented with infective pancreatic necrosis [IPN] 50% of cases had gallstones [p>0.05]. This indicated no impact of gallstone in the development of IPN. Similarly, IPN was present in 7/32 cases with alcohol consumption [p>0.05]. IPN was present in all 32 cases with cholelithiasis [p<0.05].This showed that the presence of choledocholithiasis could cause IPN. IPN was present in 7/32 cases with hypothermia [p>0.05].IPN was present in 14/32 cases with idiopathy [p>0.05].IPN was present in 13/32 cases with pancreatic or ampullary tumors [p>0.05]. Similarly, IPN was present in 10/32 cases with traumatic tumor [p>0.05] as shown in Table 2.15.

Table 2.15: Comparison of IPN with different causes

		Infective necrosis		p-value
		Present	Absent	
Gallstone	Present	16	25	0.128
	Absent	16	48	
Chronic alcohol consumption	Present	7	18	0.758
	Absent	25	55	
Choledocholithiasis	Present	32	0	0.000
	Absent	0	73	
Hypercalcemia, hyperparathyroidism	Present	14	22	0.176
	Absent	18	51	
Hypothermia	Present	7	24	0.255
	Absent	25	49	
Idiopathy	Present	14	22	0.176
	Absent	18	51	
Pancreatic or ampullary tumors	Present	13	32	0.760
	Absent	19	41	
Traumatic	Present	10	24	0.870
	Absent	22	49	

DISCUSSION:

The present retrospective study was conducted in the North Surgical Ward of Mayo Hospital, Lahore, Pakistan. The objective of the study was to determine the frequency of infected pancreatic necrosis among patients and compare the frequency of contributing factors among acute pancreatitis patients without infected pancreatic necrosis. The study showed that the most vulnerable age for pancreatitis was 21-80 years [Table 2.1]. This wide range indicates that age is not an important factor contributing to pancreatitis. However, the study suggests that gender may be an important factor where the ratio of female to male patients is almost 1:2 [Figure 2.1]. This ratio may be due to many reasons some of which are outlined as: Gallstones, Certain medications, Cigarette smoking,

Cystic fibrosis, Family history, Alcohol consumption and Hormonal changes[10].

Since gallstones are more common in male than women, this may be a significant factor contributing twice in the frequency of males than females. [11] Approximately 80% of all cases can be attributed to either gallstones or alcohol [12]. The frequency of different forms of acute pancreatitis varies markedly in different countries. Gallstones are the most common cause in the United Kingdom and Asia, whereas in the USA and Finland, alcohol is the most common causative factor. [13, 14]Cigarette smoking can also not be excluded in higher pancreatitis frequency in males than females.[13]

Necrosis in pancreatitis patients is the second stage of pathology in this disease. [15] In the present study, it was observed that necrosis was 26.7% in 28% patients. [Table 2.2]. This indicates that in most patients' pancreatitis can be cured without experiencing necrosis. Table 2.2 shows that 30-50% of the pancreatitis patients' necrosis commonly take place [17.1%] while in >50% patients, necrosis was as high as 23.8%. The table concludes that pancreatitis, if left unattended, results in high rate of necrotic tissue. In necrotizing pancreatitis, the most important risk factor resulting in death is infection of pancreatic necrosis which occurs in 40 to 70% of patients.[16] Beger and coworkers[17] have found a fourfold increase in mortality [37.8% v 8.7%] in patients with infected necrosis. Although 47% of the total patients with necrosis have positive bacteriology.

Necrosis may follow infection leading to fever. Table 5.3 shows 74.3% of the patients had fever compared with 25.7% normal body temperature. This indicates that infection is a commonplace in pancreatitis patients. This is confirmed with a higher percentage of leukocytes [Table 2.4] in 75.2% patients compared with only 24.8% of patients with normal leukocytes count. A high necrotic rate, higher leukocyte [Infection] count explains abdominal pain in 72.38% of the patients shown in [Figure 2.2] while 27.62% patients were normal.

Infection may be bacterial, fungal or viral. If pancreatitis patients are left untreated, necrosis followed by infection is an obvious endpoint. Table 5.5 shows that 33.2% of the pancreatitis patients had bacterial infection while 64.8% were without bacterial infection. [18, 19] This percentage is similar to fungal when viral infection is also taken into account and this is shown in Table 2.6.

Gallstones cause obstruction of the hepatic portal vein hindering gall fluid circulation and resulting in hepatic injury. [20] This shows that hepatic enzymes leak out into the blood indicating hepatic injury. In the present study, 39.0% [Table 2.7] of the pancreatitis patients were suffering from gallstones indicating that these are one of the major causes of pancreatitis and should be treated in conjunction with gallstones. This is supported by a high rate of pancreatitis [30.5%] in choledocholithiasis Figure 2. 3 where bile duct is obstructed with calculi.
Alcohol consumption is a known hepatic injury inducer leading to pancreatitis. [14] In the present study, 23.8% of the alcoholic patients [Table 2.8] suffered pancreatitis which is 50% less than the gall stones indicating gallstones are more important cause of pancreatitis. Hypercalcemia is a common cause of renal and gall stones and admixed with cholesterol causing bile duct obstruction.[21] In the present study 34.3% of the patients [Table 2.9] were suffering from hypercalcemia indicating that it may be causing choledocholithiasis and gall stones finally leading to pancreatitis.

Hypothermia may be caused by sepsis in the elderly. If necrosis occurs followed by infection and sepsis, hypothermia is an evident result.[22] In the present study, 29.5% of the patients [Table 2.10] suffered hypothermia suggesting that the infection had ensued in these patients and rapid treatment with antibiotics must be taken on priority. Idiopathic causes may also be important in pancreatitis patients. For example idiopathic polyneuritis, idiopathic pulmonary fibrosis, idiopathic scoliosis are important etiologies for pancreatitis patients.[23] One study has revealed that between 10 to 35% of the total cases of acute pancreatitis may be idiopathic in nature African Americans have the highest age- and sex-standardized incidence rate of idiopathic pancreatitis.[24] In another study of 51 patients had idiopathic pancreatitis. Although controversial, many authorities recommend cholecystectomy for recurrent episodes of otherwise idiopathic pancreatitis associated with biliary sludge.[25].

Table 2.11 shows that 34.3% of patients included in this study had idiopathic conditions that could be contributing to their pancreatitis condition. Table 2.12 shows the distribution of infection frequency in 30.5% pancreatitis patients and Table 2.13 shows 42.9% of the patients had pancreatic or ampullary tumors. Figure 5.4 shows 32.38% traumatic distribution frequency in pancreatic patients.

Table 2.14 shows out of 34 cases showing no pancreatic necrosis, only 2 had infection, in 28 cases

with <30% necrosis, 9 cases had infection, out of 18 cases with 30-50% necrosis 11 had infection and out of 25 cases with >50% necrosis, 10 had infection. The difference was highly significant and cases with >30% necrosis showed a high infection rate i.e. p=0.000.

Infected pancreatic necrosis is a late infective complication of acute necrotizing pancreatitis in which infection spread from the pancreas to the retroperitoneum, peripancreatic tissues and sometime in the peritoneal cavity. [26] The most common causes include gall stone and alcohol consumption and the presence of choledocholithiasis can cause infective necrosis. Infection usually occurs in 8%-12% of patients suffering from acute pancreatitis and in up to 70% with necrotizing pancreatitis.[27] In present study 50% cases with infective pancreatic necrosis were with gallstone and 50% cases were without gallstone [p>0.05], 7 cases with alcohol consumption while 25 in cases without alcohol consumption [p>0.05], 32 cases with choledocholithiasis and no patients without choledocholithiasis showed infection [p<0.05], cases with hypothermia, 25 cases with normal body temperature [p>0.05], 14 cases with idiopathy while 18 cases without idiopathy [p>0.05], 13 cases with Pancreatic or ampullary tumors while 19 in cases without Pancreatic or ampullary tumors [p>0.05] and 10 cases with traumatic tumor while 22 in cases without trauma [p>0.05] as shown in Table 2.15.

CONCLUSION:

According to the results of the present study, the prevalence of infected acute pancreatic was in 30.7% of the total patients; idiopathy, ampullary, tumor, choledocholithiasis, hypercalcemia and traumatic condition are the contributing factors in cases of severe acute pancreatitis.

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